ISIS-4823 PATENT

## What is claimed is:

1. A delayed release oral formulation for enhanced intestinal drug absorption, comprising:

- (a) a first population of carrier particles comprising said drug and a penetration enhancer, wherein said drug and said penetration enhancer are released at a first location in the intestine; and
- (b) a second population of carrier particles comprising a penetration enhancer and a delayed release coating or matrix, wherein said penetration enhancer is released at a second location in said intestine downstream from said first location, whereby absorption of said drug is enhanced when said drug reaches said second location.
- 2. The formulation of claim 1, wherein the drug is selected from the group consisting of a protein, peptide, nucleic acid, oligonucleotide, peptide hormone, antibiotic, antimicrobial agent, vasoconstrictor, cardiovascular drug, vasodilator, enzyme, bone metabolism controlling agent, steroid hormone, antihypertensive, non-steroidal antiinflammatory agent, antihistamine, antitussive, expectorant, chemotherapeutic agent, sedative, antidepressant, beta-blocker, analgesic and angiotensin converting enzyme (ACE) inhibitor.
  - 3. The formulation of claim 2, wherein said oligonucleotide is an antisense oligonucleotide.
- 4. The formulation of claim 2, wherein the penetration enhancer in (a) and (b) is the same.
- 5. The formulation of claim 2, wherein the penetration enhancer in (a) and (b) is different.
- 6. The formulation of claim 2, wherein the penetration enhancer is selected from the group consisting of a fatty acid, bile acid, chelating agent and non-chelating non-surfactant.

- 7. The formulation of claim 6, wherein said fatty acid is selected from the group consisting of arachidonic acid, oleic acid, lauric acid, capric acid, caprylic acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, a monoglyceride and a pharmaceutically acceptable salt thereof.
- 8. The formulation of claim 6, wherein said bile acid is selected from the group consisting of cholic acid, dehydrocholic acid, deoxycholic acid, glucholic acid, glycholic acid, glycholic acid, taurocholic acid, taurodeoxycholic acid, chenodeoxycholic acid, ursodeoxycholic acid, sodium tauro-24,25-dihydrofusidate, sodium glycodihydrofusidate, polyoxyethylene-9-lauryl ether and a pharmaceutically acceptable acceptable salt thereof.
- 9. The formulation of claim 6, wherein said chelating agent is selected from the group consisting of EDTA, citric acid, a salicylate, an *N*-acyl derivative of collagen, laureth-9, an *N*-amino acyl derivative of a beta-diketone and a mixture thereof.
- 10. The formulation of claim 6, wherein said non-chelating non-surfactant is selected from the group consisting of an unsaturated cyclic urea, 1-alkyl-alkanone, 1-alkenylazacycloalkanone, steroid anti-inflammatory agent and mixtures thereof.
- 11. The formulation of claim 1, wherein said formulation is a capsule, tablet, compression coated tablet or bilayer tablet.
  - 12. The formulation of claim 1, wherein said carrier particles are bioadhesive.
- 13. The formulation of claim 1, wherein aid carrier particles comprise a substance selected from the group consisting of poly-amino acids, polyimines, polyacrylates, polyalkylacrylates, polyoxethanes, polyalkylcyanoacrylates, cationized gelatins, albumins, starches, acrylates, polyethylene glycol, DEAE-derivatized polyimines, pollulans and

celluloses.

- 14. The formulation of claim 1, wherein said carrier particles comprise a material selected from the group consisting of chitosan, poly-L-lysine, polyhistidine, polyornithine, polyspermines, protamine, polyvinylpyridine, polythiodiethylamino-methylene P(TDAE), polyaminostyrene, poly(methylcyanoacrylate), poly(ethylcyanoacrylate), poly(butylcyanoacrylate), poly(isobutylcyanoacrylate), poly(isohexylcyanoacrylate), DEAE-methacrylate, DEAE-ethyhexylacrylate, DEAE-acrylamide, DEAE-albumin, DEAE-dextran, polymethylacrylate, polyhexylacrylate, poly (D,L-lactic acid), poly (DL-lactic-coglycolic acid) (PLGA) and polyethylene glycol (PEG).
  - 15. The formulation of claim 1, wherein said carrier particles are cationic.
- 16. The formulation of claim 15, wherein said carrier particles comprise a complex of poly-L-lysine and alginate, a complex of protamine and alginate, lysine, dilysine, trilysine, calcium, albumin, glucosamine, arginine, galactosamine, nicotinamide, creatine, lysine-ethyl ester and arginine ethyl-ester.
- 17. The formulation of claim 1 wherein said delayed release coating or matrix is selected from the group consisting of acetate phthalate, propylene glycol, sorbitan monoleate, cellulose acetate phthalate (CAP), cellulose acetate trimellitate, hydroxypropyl methyl cellulose phthalate (HPMCP), methacrylates, chitosan, guar gum and polyethylene glycol (PEG).
- 18. A method for enhancing the absorption of a drug in an animal, comprising administering the pharmaceutical formulation of claim 1 to said animal.
  - 19. The method of claim 18, wherein said animal is a mammal.
  - 20. The method of claim 19, wherein said mammal is a human.